



Larsen syndrome

Larsen syndrome is a disorder that affects the development of bones throughout the body. The signs and symptoms of Larsen syndrome vary widely even within the same family. Affected individuals are usually born with inward- and upward-turning feet (clubfeet) and dislocations of the hips, knees, and elbows. They generally have small extra bones in their wrists and ankles that are visible on x-ray images. The tips of their fingers, especially the thumbs, are typically blunt and square-shaped (spatulate).

People with Larsen syndrome may also have an unusually large range of joint movement (hypermobility) and short stature. They can also have abnormal curvature of the spine (kyphosis or scoliosis) that may compress the spinal cord and lead to weakness of the limbs.

Characteristic facial features include a prominent forehead (frontal bossing), flattening of the bridge of the nose and of the middle of the face (midface hypoplasia), and wide-set eyes (ocular hypertelorism). Some people with Larsen syndrome have an opening in the roof of the mouth (a cleft palate) or hearing loss caused by malformations in the tiny bones in the ears (ossicles). Some affected individuals experience respiratory problems as a result of weakness of the airways that can lead to partial closing, short pauses in breathing (apnea), and frequent respiratory infections. People with Larsen syndrome can survive into adulthood and intelligence is unaffected.

Frequency

Larsen syndrome occurs in approximately 1 in 100,000 newborns.

Genetic Changes

Mutations in the *FLNB* gene cause Larsen syndrome. The *FLNB* gene provides instructions for making a protein called filamin B. This protein helps build the network of protein filaments (cytoskeleton) that gives structure to cells and allows them to change shape and move. Filamin B attaches (binds) to another protein called actin and helps the actin to form the branching network of filaments that makes up the cytoskeleton. It also links actin to many other proteins to perform various functions within the cell, including the cell signaling that helps determine how the cytoskeleton will change as tissues grow and take shape during development.

Filamin B is especially important in the development of the skeleton before birth. It is active (expressed) in the cell membranes of cartilage-forming cells (chondrocytes). Cartilage is a tough, flexible tissue that makes up much of the skeleton during early development. Most cartilage is later converted to bone (a process called ossification), except for the cartilage that continues to cover and protect the ends of bones and

is present in the nose, airways (trachea and bronchi), and external ears. Filamin B appears to be important for normal cell growth and division (proliferation) and maturation (differentiation) of chondrocytes and for the ossification of cartilage.

FLNB gene mutations that cause Larsen syndrome change single protein building blocks (amino acids) in the filamin B protein or delete a small section of the protein sequence, resulting in an abnormal protein. This abnormal protein appears to have a new, atypical function that interferes with the proliferation or differentiation of chondrocytes, impairing ossification and leading to the signs and symptoms of Larsen syndrome.

Inheritance Pattern

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In some cases, an affected person inherits the mutation from one affected parent. Other cases result from new mutations in the gene and occur in people with no history of the disorder in their family.

Autosomal recessive inheritance of Larsen syndrome has been reported in a small number of families. Autosomal recessive means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. In some of these cases, the appearance of autosomal recessive inheritance may actually result from multiple siblings in a family each inheriting a single altered gene from an unaffected parent who has an *FLNB* mutation only in some or all of their sperm or egg cells. When a mutation is present only in reproductive cells, it is known as germline mosaicism.

A few rarer conditions with overlapping signs and symptoms and autosomal recessive inheritance have sometimes been diagnosed as Larsen syndrome, but they are now generally considered to be different disorders because they are typically more severe and are not caused by *FLNB* gene mutations.

Other Names for This Condition

- LRS

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Larsen syndrome
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0175778/>
- Genetic Testing Registry: Larsen syndrome, dominant type
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1835564/>

Other Diagnosis and Management Resources

- GeneReview: FLNB-Related Disorders
<https://www.ncbi.nlm.nih.gov/books/NBK2534>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Health Topic: Bone Diseases
<https://medlineplus.gov/bonediseases.html>
- Health Topic: Hearing Disorders and Deafness
<https://medlineplus.gov/hearingdisordersanddeafness.html>
- Health Topic: Scoliosis
<https://medlineplus.gov/scoliosis.html>

Genetic and Rare Diseases Information Center

- Larsen syndrome
<https://rarediseases.info.nih.gov/diseases/6860/larsen-syndrome>

Educational Resources

- Disease InfoSearch: Larsen syndrome
<http://www.diseaseinfosearch.org/Larsen+syndrome/4093>
- MalaCards: larsen syndrome
http://www.malacards.org/card/larsen_syndrome
- Orphanet: Autosomal dominant Larsen syndrome
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=503
- University of Washington Neuromuscular Disease Center
<http://neuromuscular.wustl.edu/spinal/fsp.html#larsen>

Patient Support and Advocacy Resources

- Children's Craniofacial Association
<http://www.ccakids.com/>
- International Skeletal Dysplasia Registry, UCLA
<http://ortho.ucla.edu/isdr>
- National Organization for Rare Disorders
<https://rarediseases.org/rare-diseases/larsen-syndrome/>
- The MAGIC Foundation for Children's Growth
<https://www.magicfoundation.org/>

GeneReviews

- FLNB-Related Disorders
<https://www.ncbi.nlm.nih.gov/books/NBK2534>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28larsen+syndrome%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D>

OMIM

- LARSEN SYNDROME
<http://omim.org/entry/150250>
- MULTIPLE JOINT DISLOCATIONS, SHORT STATURE, AND CRANIOFACIAL DYSMORPHISM WITH OR WITHOUT CONGENITAL HEART DEFECTS
<http://omim.org/entry/245600>

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